Anormalità del controllo nervoso cardiovascolare nella fibromialgia: implicazioni sui meccanismi del dolore e della tolleranza ortostatica

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Disclosure: none
Key points

• Fibromyalgia epidemiology and clinical features

• Cardiovascular autonomic abnormalities in Fibromyalgia

• Orthostatic Intolerance and Pain: the role of autonomic nervous system

• Therapeutic approach based on pathophysiology
• Fibromyalgia is diagnosed in patients with **chronic widespread pain** and/or multiple muscular tender points on examination.

• Chronic widespread pain is defined as pain for at least three months, affecting both sides of the body, both above and below the waist.

*BMJ* 2014; 348 doi: http://dx.doi.org/10.1136/bmj.g1224
Prevalence of fibromyalgia (new diagnostic criteria):

• 2-6 %, higher in women

• The prevalence rises steadily with age, with a maximum prevalence in the over 60s.
   

• Fibromyalgia is not restricted to developed countries.
   Bangladesh 4.4% of people in a rural village, 3.2% in a poor city area, 3.3% in a wealthy urban area.
   
   *Haq SA et al J Rheumatol 2005;32:348-53*

• About 15 million persons are affected by FM in the USA.
Fig 1 Flow chart for diagnosis of fibromyalgia.

How long has the pain been present?

>3 months

- Is the pain widespread?*
  - Yes
    - Are there clinical features of specific autoimmune diseases, such as inflamed joints, photosensitive rash, or Raynaud's syndrome?
      - Yes
        - Urea and electrolytes, liver function tests, calcium, phosphate, C reactive protein, erythrocyte sedimentation rate, and autoantibody tests (such as ANA, RhF) (all normal in fibromyalgia)
          - Note: Even if tests show another diagnosis the patient can have a diagnosis of fibromyalgia in addition
      - No
        - Simple blood tests only (urea and electrolytes, liver function tests, calcium, phosphate, C reactive protein, and erythrocyte sedimentation rate) (all normal in fibromyalgia)

  - No

- <3 months

Not fibromyalgia

Are there symptoms of unrefreshing sleep, fatigue, or difficulty concentrating?

Fibromyalgia

Palpation for muscular tender points is optional but may help validate diagnosis for patient

Anisur Rahman et al. BMJ 2014;348:bmj.g1224
• The primary disorder in FM seems to be a change in some central mechanism of pain control, possibly resulting from a neurotransmitter dysfunction:

  - an inhibitory neurotransmitter deficiency in spinal or supraspinal levels
  - an excitatory neurotransmitter hyperactivity

• These dysfunctions could be triggered by a nonspecific stress, such as a viral infection, psychological stress, or physical trauma.
**Figure 1** Pathways of pain processing implicated in chronic pain and fibromyalgia

Schmidt-Wilcke, T. & Clauw, D. J. (2011) Fibromyalgia: from pathophysiology to therapy
The hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, are implicated in the pathophysiology of FM.

Associated symptoms: chronic fatigue, un-refreshing sleep, anxiety, cognitive dysfunction, syncope and pre-syncope.
Key points

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• Therapeutic approach based on pathophysiology
Abnormalities of Cardiovascular Neural Control and Reduced Orthostatic Tolerance in Patients with Primary Fibromyalgia

RAFFAELLO FURLAN, SIMONA COLOMBO, FRANCESCA PEREGO, FABIOLA ATZENI, ALESSANDRO DIANA, FRANCA BARBIC, ALBERTO PORTA, FABIO PACE, ALBERTO MALLIANI, and PIERCARLO SARZI-PUTTINI

(J Rheumatol 2005;32:1787–93)

Population: 13 FM (44± 3 years)
15 Control (37± 4 years)

Variables: ECG
BP
RESP
MSNA

Protocol: Rest (15’), Tilt 15° incremental (5 min) up to 75° head-up, 20 minutes

Methodology: Autoregressive spectrum and cross-spectrum analysis techniques provides indices of cardiac and vascular autonomic profile LF_{RR}, HF_{RR}, LF/HF, LF_{SAP}

Integrated MSNA burst/min – burst/100beats
Spectral Indices of Cardiovascular Autonomic Control

**LF** \(_{RR}\) index on cardiac sympathetic modulation

**HF** \(_{RR}\) index of cardiac vagal modulation

**LF/HF** index of instantaneous sympathovagal modulation to the heart

**LF** \(_{SAP}\) index of sympathetic modulation to the vessels
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration, yrs</td>
<td>62.5</td>
</tr>
<tr>
<td>Pain visual analog scale (0–100)</td>
<td>12.5</td>
</tr>
<tr>
<td>No. of tender points</td>
<td>12.5</td>
</tr>
<tr>
<td>Health Assessment Questionnaire (0–3)</td>
<td>12.5</td>
</tr>
<tr>
<td>Fatigue (0–100)</td>
<td>12.5</td>
</tr>
</tbody>
</table>
• Patients with fibromyalgia seemed to be characterized by a global increase of central cardiovascular sympathetic activity while recumbent.

Furlan R et al J Reumatol 2005; 32:1787-93
Table 3. Indices of autonomic activity in study subjects at rest and during tilt test. Due to reduced RR variance, LF<sub>RR</sub> in ms<sup>2</sup> is unchanged during tilt test, whereas it increases in NU<sup>35</sup>.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th></th>
<th>Tilt</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>FM</td>
<td>Controls</td>
<td>FM</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>12 ± 2</td>
<td>22 ± 2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>27 ± 3&lt;sup&gt;†&lt;/sup&gt;</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Bursts/100 beats</td>
<td>19 ± 2</td>
<td>31 ± 4&lt;sup&gt;*&lt;/sup&gt;</td>
<td>32 ± 3&lt;sup&gt;†&lt;/sup&gt;</td>
<td>34 ± 5</td>
</tr>
<tr>
<td>NE, pg/ml</td>
<td>266 ± 25</td>
<td>264 ± 32</td>
<td>496 ± 36&lt;sup&gt;†&lt;/sup&gt;</td>
<td>590 ± 90&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>E, pg/ml</td>
<td>31 ± 7</td>
<td>34 ± 7</td>
<td>64 ± 11&lt;sup&gt;†&lt;/sup&gt;</td>
<td>75 ± 13&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>RR σ&lt;sup&gt;2&lt;/sup&gt;, ms&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2390 ± 601</td>
<td>1186 ± 268</td>
<td>1292 ± 267&lt;sup&gt;†&lt;/sup&gt;</td>
<td>786 ± 166&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>LF&lt;sub&gt;RR&lt;/sub&gt;, ms&lt;sup&gt;2&lt;/sup&gt;</td>
<td>579 ± 111</td>
<td>573 ± 139</td>
<td>499 ± 119</td>
<td>476 ± 130</td>
</tr>
<tr>
<td>NU</td>
<td>49.5 ± 4.6</td>
<td>66.5 ± 4.5&lt;sup&gt;*&lt;/sup&gt;</td>
<td>81.8 ± 2.6&lt;sup&gt;†&lt;/sup&gt;</td>
<td>87.8 ± 1.9&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>HF&lt;sub&gt;RR&lt;/sub&gt;, ms&lt;sup&gt;2&lt;/sup&gt;</td>
<td>939 ± 365</td>
<td>198 ± 51&lt;sup&gt;*&lt;/sup&gt;</td>
<td>82.6 ± 21.9&lt;sup&gt;†&lt;/sup&gt;</td>
<td>52 ± 15&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>NU</td>
<td>46.0 ± 4.4</td>
<td>25.4 ± 3.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>14.1 ± 2.8&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8.6 ± 1.6&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.46 ± 0.3</td>
<td>3.7 ± 0.7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10.0 ± 1.9&lt;sup&gt;†&lt;/sup&gt;</td>
<td>16.3 ± 2.5&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>SAP σ&lt;sup&gt;2&lt;/sup&gt;, mm/Hg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>11.9 ± 3</td>
<td>12.6 ± 3.6</td>
<td>21.6 ± 4.9</td>
<td>21.4 ± 3.8</td>
</tr>
<tr>
<td>LF&lt;sub&gt;SAP&lt;/sub&gt;, mm/Hg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.2 ± 0.5</td>
<td>6.3 ± 2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>12.3 ± 3.8&lt;sup&gt;†&lt;/sup&gt;</td>
<td>10.2 ± 1.7</td>
</tr>
</tbody>
</table>

MSNA: muscle sympathetic nerve activity, NE: norepinephrine, E: epinephrine, σ<sup>2</sup>: variance, LF<sub>RR</sub>: low frequency component of RR variability, HF<sub>RR</sub>: high frequency component of RR variability, NU: normalized units, LF<sub>SAP</sub>: low frequency component of systolic arterial pressure variability. * p < 0.05, controls vs FM patients. † p < 0.05 rest vs tilt.
Key points

• Fibromyalgia epidemiology and clinical features

• Cardiovascular autonomic abnormalities in Fibromyalgia

• Orthostatic Intolerance and Pain: the role of autonomic nervous system

• Therapeutic approach based on pathophysiology
In patients with fibromyalgia we observed a lack of increase of MSNA and $L F_{S A P}$ in response to gravitational stimulus associated to reduced decrease of $H F_{R R}$ index of vagal modulation to the heart.

Furlan R et al J Reumatol 2005; 32:1787-93
Vaso-vagal event free [%]

Time [min]

----- FM
____ Controls

Furlan R et al J Reumatol 2005; 32:1787-93
In FM pain intensity seemed to be linearly correlated with the indeces of cardiovascular sympathetic modulation and to the sympathetic neural discharge to the vessels.
**Table I.** Clinical features of patients with FMS.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FMS (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>23/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.7 ± 12.3</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.7 ± 4.9</td>
</tr>
<tr>
<td>No. of tender points (0–18)</td>
<td>14.1 ± 2.0</td>
</tr>
<tr>
<td>Pain visual analogue scale (0–100 mm)</td>
<td>66.1 ± 14.7</td>
</tr>
<tr>
<td>Fatigue (0–100 mm)</td>
<td>58.7 ± 20.3</td>
</tr>
<tr>
<td>Health Assessment Questionnaire (0–3)</td>
<td>0.74 ± 0.57</td>
</tr>
</tbody>
</table>

**Visual Analogue Scales**

0 pain  

Pain as bad as it could possibly be  

100
Key points

• Fibromyalgia epidemiology and clinical features

• Cardiovascular autonomic abnormalities in Fibromyalgia

• Orthostatic Intolerance and Pain: the role of autonomic nervous system

• Therapeutic approach based on pathophysiology
• The use of anti adrenergic agents such as clonidine might lessen chronic pain intensity by reducing the underlying excessive sympathetic activity.

(Davis KD et al, Pain 1991, 47:309-17)

• The physical exercise, by reducing cardiovascular sympathetic activity at rest might be useful in FM patient’s pain control and might improve orthostatic intolerance.
## Effects of a hydrotherapy programme on symbolic and complexity dynamics of heart rate variability and aerobic capacity in fibromyalgia patients


### Population:
- 20 FM
- 20 Controls

### Variables:
- EKG – pain intensity – quality of life (FIQ)

### Protocol:
- REST and STAND
- Before and after 16 weeks of hydrotherapy program

### Methodology:
- The heart rate variability was analized by linear (spectral analysis) and non linear (symbolic analysis) techniques
  - \( \text{LF}_{\text{RR}} - \text{HF}_{\text{RR}} - \text{LF/HF} \)
  - \( 2\text{UV} \% \) (index of vagal modulation to the heart)
  - \( 0\text{V} \% \) (index of sympathetic modulation to the heart)
  - Shannon Entropy (SE) e Complexity Index (CI)
**Fig. 2.** Clinical features assessed at Baseline and Post16. FIQ: Fibromyalgia Impact Questionnaire; TP: tender points; VAS: visual analogue scale; PPT: pressure pain threshold.
**Table II.** HRV analyses in healthy controls and in the FMS patients at baseline and Post16. Data are expressed as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>FMS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SUP</td>
<td>STAND</td>
<td>SUP</td>
<td>STAND</td>
</tr>
<tr>
<td><strong>Linear analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\mu_{RR}$ (ms)</td>
<td>899.4 ± 22.9</td>
<td>810.1 ± 23.8</td>
<td>805.4 ± 23.2</td>
<td>709.5 ± 23.6</td>
</tr>
<tr>
<td>$\sigma^2_{RR}$ (ms$^2$)</td>
<td>1505.5 ± 346.1</td>
<td>1338.9 ± 263.8</td>
<td>475.4 ± 113.2</td>
<td>354.7 ± 103.5</td>
</tr>
<tr>
<td>HF (ms$^2$)</td>
<td>508.2 ± 141.8</td>
<td>281.8 ± 75.7</td>
<td>89.2 ± 19.1</td>
<td>30.0 ± 6.4</td>
</tr>
<tr>
<td>HFnu (%)</td>
<td>55.4 ± 3.3</td>
<td>36.9 ± 3.4</td>
<td>43.0 ± 3.8</td>
<td>23.6 ± 2.8</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.89 ± 0.1</td>
<td>2.22 ± 0.33</td>
<td>1.83 ± 0.31</td>
<td>4.35 ± 0.6</td>
</tr>
<tr>
<td><strong>Non-linear analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0V (%)</td>
<td>12.7 ± 1.6</td>
<td>28.2 ± 3.2</td>
<td>22.5 ± 2.9</td>
<td>34.8 ± 2.3</td>
</tr>
<tr>
<td>1V (%)</td>
<td>49.1 ± 1.4</td>
<td>46.8 ± 1.0</td>
<td>48.8 ± 1.3</td>
<td>46.0 ± 0.8</td>
</tr>
<tr>
<td>2LV (%)</td>
<td>14.4 ± 1.2</td>
<td>9.9 ± 1.6</td>
<td>10.1 ± 1.1</td>
<td>6.4 ± 1.0</td>
</tr>
<tr>
<td>2UV (%)</td>
<td>23.7 ± 2.5</td>
<td>15.1 ± 1.8</td>
<td>18.7 ± 2.0</td>
<td>12.8 ± 1.6</td>
</tr>
<tr>
<td>SE</td>
<td>3.80 ± 0.10$^a$</td>
<td>3.40 ± 0.11</td>
<td>3.40 ± 0.10</td>
<td>3.40 ± 0.06</td>
</tr>
<tr>
<td>CI</td>
<td>1.15 ± 0.03$^a$</td>
<td>1.02 ± 0.04</td>
<td>1.01 ± 0.04</td>
<td>0.98 ± 0.03</td>
</tr>
</tbody>
</table>

*p<0.05 HC Baseline SUP vs. FMS Baseline SUP; $^a$p<0.05 HC Baseline SUP vs. HC Baseline STAND; $^b$p<0.05 FMS Baseline SUP vs. FMS Post16 SUP; $^c$p<0.05 FMS Post16 SUP vs. FMS Post16 STAND. Significant main effects are described in the results. HRV: heart rate variability; STAND: active standing; SUP: supine position; FMS: fibromyalgia syndrome; $\mu$: mean of RR; $\sigma^2$: variance of RR; HF: high frequency component of RR variability expressed in absolute units; HFnu: high frequency component of RR variability expressed in normalised units; 0V: patterns with no variation; 1V: patterns with one variation; 2LV: patterns with two like variations; 2UV: patterns with two unlike variations. SE: Shannon entropy; CI: complexity index.

0V% is an index of cardiac sympathetic modulation
2UV% is an index of cardiac parasympathetic modulation
Conclusions

FM patients are characterized by an exaggerated sympathetic drive to the heart and to the vessels compared to healthy subjects.

The pain intensity is directly related to the cardiovascular sympathetic activity.

A blunted enhancement of sympathetic modulation to the vessels and impaired cardiac vagal withdrawal during a gravitational stress, may account for the excessive rate of syncope and presyncope.

The reduction of sympathetic overactivity by the anti-adrenergic drugs and the specific physical exercise may reduce pain intensity and improve the orthostatic tolerance of FM patient.

The indeces (spectral and non-linear analysis) of cardiovascular autonomic profile may represent non-invasive, low-cost bio-markers to follow the effect of therapy in these subjects.